THE THREAT OF BISPHENOL A TO MAMMAL REPRODUCTION

Universitat Autònoma de Barcelona

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Context: Bisphenol A (BPA) is an endocrine disruptor contaminant present in plastics that has been associated with several pathologies, such as obesity, diabetes, and thyroid disorders, among others. Ingestion of contaminated food is the main route of exposure.

Objectives: evaluate the evidence concerning the effects of BPA on male and female gonads and their consequences. Some potential therapeutic/preventive agents are also reviewed.

MALE

Figure 1. Testicular weight of male rats exposed to different doses of BPA by oral gavage. Modified from Osman et al., (2021).

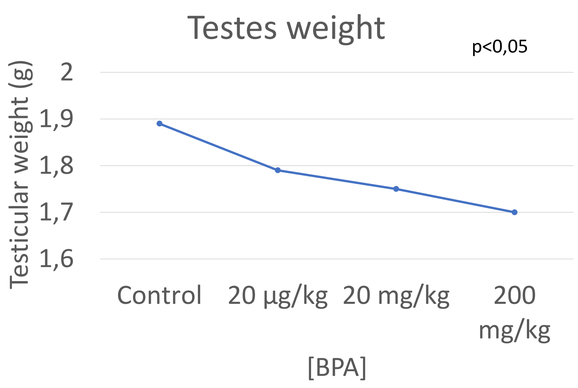


Figure 2. Serum testosterone (T) levels of male rats following oral administration of 5, 50, and 100 µg of BPA/100 mg body weight. Modified from Srivastava and Gupta, (2018).

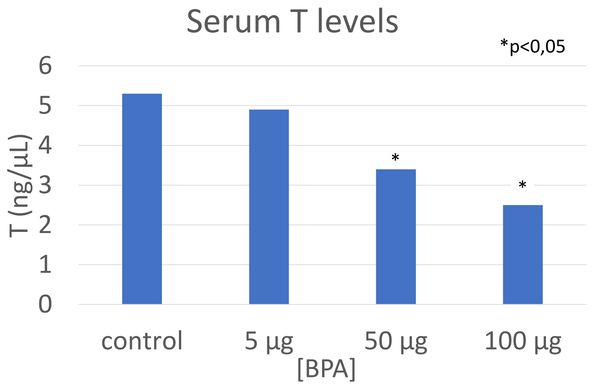


Table 1. Results of different studies regarding **sperm quality parameters.**

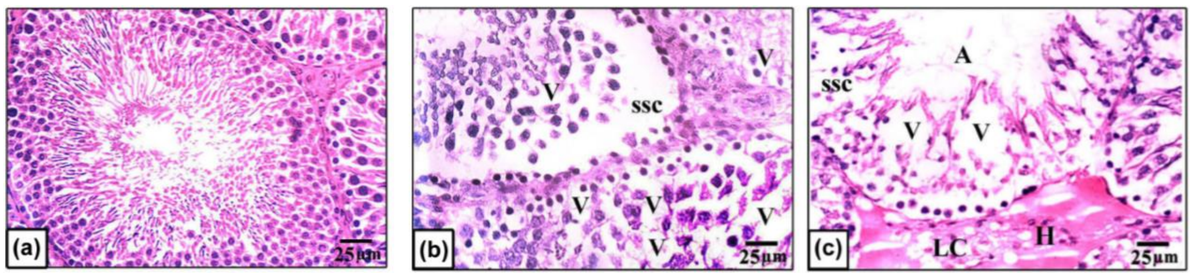
	[sperm] or sperm count	Sperm motility	Sperm morphology	pH
Jiang et al., 2016	↓		Abnormal	
Kaur et al., 2018	↓	↓		
Liu et al., 2013	↓	=	-	
Othman et al., 2016	↓	↓	Abnormal	
Park et al., 2020		↓ (fresh)		↑
Qiu et al., 2013	↓	=		
Srivastava and Gupta, 2018	↓			
Wu et al., 2020	=	=		
Yildiz-Gulay et al., 2020	↓	↓		=

Table 2. Results of different studies relating to **steroidogenic enzymes and androgen receptor (AR).**

	StAR	Cyp450scc	Cyp450c17	3β-HSD	17β-HSD	Cyp450arom	AR
Qiu et al., 2013	↑	↑		↓	↓	↓	↓
Jiang et al., 2016	↓	↓	↓	↓	↓		
Zhang et al., 2018	↓	↓	↓	↓			
de Freitas et al., 2016							↓

Abbreviations: StAR, steroidogenic acute regulatory protein; Cyp450scc, cytochrome P450 cholesterol side-chain cleavage enzyme; Cyp450arom, cytochrome P450 aromatase; Cyp45017c, cytochrome P450 family 17; 3β-HSD, 3β-hydroxysteroid dehydrogenase; 17β-HSD, 17β-hydroxysteroid dehydrogenase.

Figure 3. Histopathology of testes (Othman et al., 2016).



(a) Testis section of control rat showing well-developed seminiferous tubules with active spermatogenesis and prominent interstitial cellularity. (b) Testis section of 3-week BPA-injected rats illustrating vacuolization (V) and sloughing of spermatogenic cells (SSC). (c) Testis section of 6-week BPA-injected rats showing atrophy of the seminiferous tubules (A); marked vacuolization (V); sloughing of spermatogenic cells (SSC); interstitial hemorrhage (H); and vacuolated, degenerated, and poorly developed Leydig cells (LC).

POTENTIAL PREVENTIVE AGENTS

Table 4. Summary of the effects of some **potential preventive/therapeutic agents in male**.

	MLT	Vit E	Se	CT	ECH	Boron	Punicalagin	Rosewater	Clove oil
↑[sperm] or nº	X	X	X	X	X		X		
↑serum [T]	X	X		X	X			X	X
↓the nº of apoptotic cells	X	X	X						
↑ sperm motility	X		X	X	X		X		
Normal sperm morphology	X								
↑ [FSH] and [LH]				X	X				
↓ [MDA] and ↑ SOD and CAT levels	X					X	X		
↑ testes weight								X	X

Abbreviations: T, testosterone; FSH, follicle stimulating hormone; LH, luteinizing hormone; MDA, malondialdehyde; SOD, superoxide dismutase, CAT, catalase; MLT, melatonin; Vit E, vitamin E; Se, selenium; CT, *Cistanche tubulosa*; ECH, Echinacoside.

FEMALE

Figure 4. Ovarian weight of female rats neonatally exposed to 50 and 100 µg of BPA/50 µL. Modified from Fernández et al., (2010).

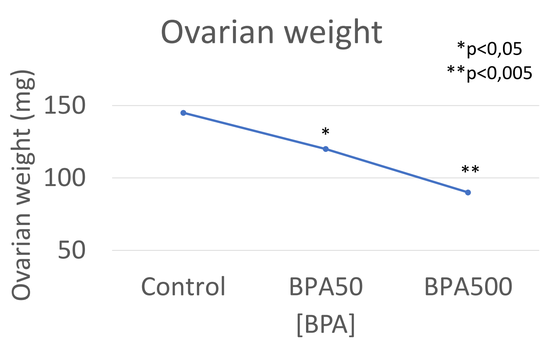


Figure 5. Effect of BPA exposure during pregnancy on the **mice pups' survival rate** (Wei et al., 2020).

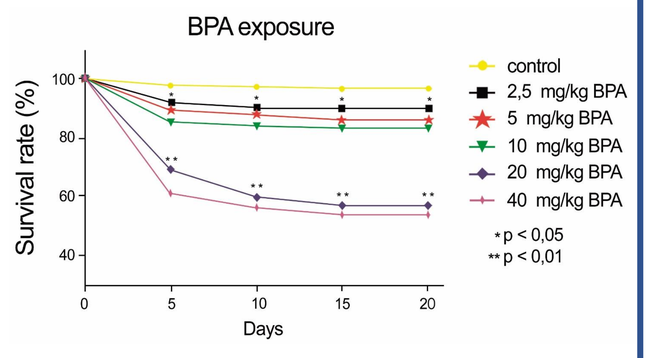


Table 3. Results of different studies relating to **hormone levels**.

	Exposure		[FSH]	[LH]	[E2]	[T]	[P4]
Srivastava and Dhagga, 2019	Adult		↓		↓		↓
Osman et al., 2021	Adult		↓		↑		↑
Wei et al., 2020	Prenatal	PND 21	↓	↑	↓		↓
		PND 56	↓	↓	↓		↓
Peretz et al., 2011	In vitro				↓	↓	↓
Mahalingam et al., 2017	Prenatal	F1			↓	=	=
		F2			=	↓	=
Fernández et al., 2010	Neonatal				↑	↑	↓
Hu et al., 2018	Adult				↑	↑	=

Abbreviations: PND, postnatal day; F1, F1 generation; F2, F2 generation; FSH, follicle stimulating hormone; LH, luteinizing hormone; E2, oestradiol; T, testosterone; P4, progesterone.

Figure 6. Apoptosis detected by TUNEL assay in 50 mg/kg BPA-exposed mice ovaries. DAPI dyes nuclei. The apoptotic signal (green) was positive in granulosa cells and oocytes. Bar: 50 µm (Zhu et al., 2018).

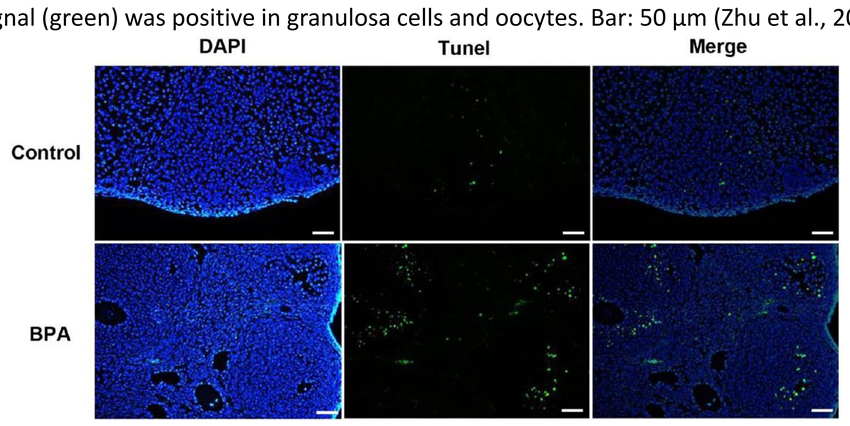
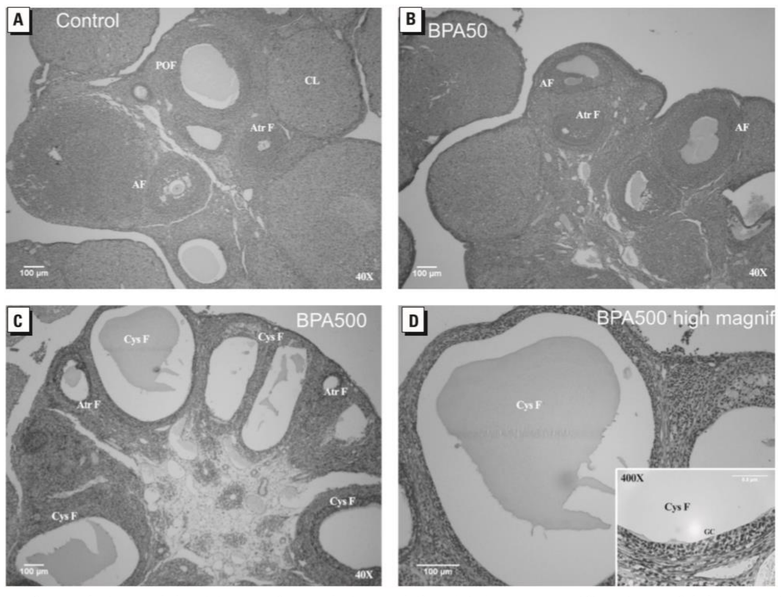


Figure 7. Histopathology of adult rat ovaries neonatally exposed to BPA (Fernández et al., 2010).



(a) Control. (b) 50 µg of BPA/50 µL. (c) 500 µg of BPA/50 µL. (d) A higher magnification of (c), showing a cystic follicle in detail; the inset shows the thin granulosa layer and nondetectable theca in the follicle. Abbreviations: AF, antral follicles; Atr F, atretic follicles; CL, corpus luteum; GC, granulosa cell; POF, preovulatory follicles; Cys F, cystic follicle.

CONCLUSIONS

All the alterations observed lead to a possible subfertility or infertility in both genders, therefore, BPA can be considered as a threat to mammal reproduction, apart from other pathologies associated.

The use of potential preventive or therapeutic agents may mitigate or even revert BPA-induced damage.

Avoiding the use of BPA as a component of plastics would be a suitable solution, especially in food storage and water containers.